

## PCT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

**NOTIFICATION CONCERNING  
SUBMISSION OR TRANSMITTAL  
OF PRIORITY DOCUMENT**

(PCT Administrative Instructions, Section 411)

To:

TABUSHI, Eiji  
Fujisawa Pharmaceutical Co., Ltd.  
Osaka Factory  
1-6, Kashima 2-chome  
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Osaka 532-8514  
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|  |  |
|--|--|
| Date of mailing (day/month/year)<br>01 October 1999 (01.10.99)       |  |
| Applicant's or agent's file reference<br>PWO-18725                   | <b>IMPORTANT NOTIFICATION</b>  |
| International application No.<br>PCT/JP99/04978                      | International filing date (day/month/year)<br>10 September 1999 (10.09.99) |
| International publication date (day/month/year)<br>Not yet published | Priority date (day/month/year)<br>14 September 1998 (14.09.98)             |
| Applicant<br>FUJISAWA PHARMACEUTICAL CO., LTD. et al                 |  |

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

| <u>Priority date</u>    | <u>Priority application No.</u> | <u>Country or regional Office<br/>or PCT receiving Office</u> | <u>Date of receipt<br/>of priority document</u> |
|-------------------------|---------------------------------|---|---|
| 14 Sept 1998 (14.09.98) | PP5841                          | AU  | 27 Sept 1999 (27.09.99)                         |

|  |   |
|--|---|
| <p align="center">The International Bureau of WIPO<br/>34, chemin des Colombettes<br/>1211 Geneva 20, Switzerland</p> <p>Facsimile No. (41-22) 740.14.35</p> | <p>Authorized officer</p> <p align="center">M. Sakai</p> <p>Telephone No. (41-22) 338.83.38</p> |
|--|---|

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|  |   |  |
|--|---|--|
| Applicant's or agent's file reference<br><b>PWO - 18725</b>  | <b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |  |
| International application No.<br><b>PCT/JP 99/04978</b>      | International filing date (day/month/year)<br><b>10/09/1999</b>   | (Earliest) Priority Date (day/month/year)<br><b>14/09/1998</b> |
| Applicant<br><b>FUJISAWA PHARMACEUTICAL CO., LTD et. al.</b> |   |  |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.  
☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

**4. With regard to the title,**

- ☐ the text is approved as submitted by the applicant.
- ☒ the text has been established by this Authority to read as follows:

**NEW USE OF IMMUNOSUPPRESSANTS FOR MMP-MEDIATED DISEASES**

**5. With regard to the abstract,**

- ☐ the text is approved as submitted by the applicant.
- ☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.

☐ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 99/04978

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 4, 6, 9  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 4, 6, 9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: -  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

A new use of immunosuppressant for treating or preventing MMP-mediated diseases is provided.

The preferred immunosuppressants are tacrolimus, cyclosporin A or 33-epi-chloro-33-desoxyascomycin (pimecrolimus).

Particularly, preferable MMP-mediated diseases are the diseases or conditions caused by gelatinase and/or collagenase, and/or inflammatory diseases concerned with gelatinase; such as arthritis (e.g., osteoarthritis, rheumatoid arthritis, etc.), cerebral diseases (e.g., stroke, etc.), tissue ulceration (e.g., corneal, epidermal and gastric ulceration, etc.), abnormal wound healing, periodontal diseases, bone diseases (e.g., Paget's diseases, osteoporosis, etc.), tumor growth, tumor metastasis or invasion, HIV-infection, decubitus, decubitus ulcer, restenosis, epidermolysis bullosa, sepsis, septic shock, neoplasm, psoriasis, neovascularization and multiple sclerosis.

## INTERNATIONAL SEARCH REPORT

International Application No.

JP 99/04978

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K31/435 A61K38/13

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| X          | KATO, TAKASHI: "Effect of immunosuppressant drug (FK 506 and cyclosporin) on gingival fibroblasts" NIPPON SHISHUBYO GAKKAI KAISHI (1995), 37(2), 211-223, 1995, XP000905245 abstract   | 1-9                   |
| X          | TOCCI, MICHAEL J. ET AL: "The immunosuppressant FK506 selectively inhibits expression of early T cell activation genes" J. IMMUNOL. (1989), 143(2), 718-26, 1989, XP000906772 abstract | 1-9                   |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

2 May 2000

Date of mailing of the international search report

19/05/2000

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

A. Jakobs

## INTERNATIONAL SEARCH REPORT

Intel. Application No.  
JP 99/04978

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| X          | ARITA, C. ET AL: "Inhibition by FK506 of established lesions of collagen-induced arthritis in rats"<br>CLIN. EXP. IMMUNOL. (1990), 82(3), 456-61<br>1990, XP000904902<br>abstract   | 1-9                   |
| X          | KOCH, K. ET AL: "CP-123,369: a potent, orally active immunosuppressive agent"<br>INFLAMMATION RES. (1995), 44(SUPPL. 2), S183-S184, 1995, XP000904905<br>the whole document   | 1-9                   |
| X          | SUGIYAMA, EIJI ET AL: "FK506, an immunosuppressant, partially inhibits interleukin 6 production by adherent rheumatoid synovial cells"<br>J. RHEUMATOL. (1994), 21(9), 1597-601, 1994, XP000904906<br>abstract  | 1-9                   |
| X          | GRIFFITHS, R. J. ET AL: "Characterization of passively transferred antigen arthritis induced by methylated bovine serum albumin in the rat: effect of FK 506 on arthritis development"<br>AGENTS ACTIONS (1992), 36(1-2), 146-51, 1992, XP000904904<br>abstract | 1-9                   |
| X          | ZENIYA, AKIRA ET AL: "Anti- ulcer effect of FK 506, immunosuppressive agent, in rats"<br>J. GASTROENTEROL. (1994), 29(3), 383-4, 1994, XP000904975<br>the whole document  | 1-9                   |
| X          | WO 91 17754 A (FUJISAWA PHARMACEUTICAL CO)<br>28 November 1991 (1991-11-28)<br>abstract<br>page 2, line 5-29<br>page 5, line 1 -page 11, line 11; claims 1-19   | 1-9                   |
| X          | KARASHIMA, TADASHI ET AL: "FK 506 and cyclosporin A inhibit growth factor-stimulated human keratinocyte proliferation by blocking cells in the G0/G1 phases of the cell cycle"<br>J. DERMATOL. SCI. (1996), 12(3), 246-254, 1996, XP000904978<br>abstract       | 1-9                   |

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# INTERNATIONAL SEARCH REPORT

Inte      onal Application No  
JP 99/04978

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| X          | MROWIETZ, U. ET AL: "The novel ascomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion"<br>BR. J. DERMATOL. (1998), 139(6), 992-996 ,<br>1998, XP000904979<br>abstract; figure 1  | 1-7                   |
| X          | BUTCHER, STEVEN P. ET AL:<br>"Neuroprotective actions of FK506 in experimental stroke: in vivo evidence against an antiexcitotoxic mechanism"<br>J. NEUROSCI. (1997), 17(18), 6939-6946 ,<br>1997, XP000904977<br>abstract  | 1-9                   |
| X          | INABA, HIROYUKI ET AL: "Effect of indomethacin and tacrolimus hydrate on the healing process of experimental gastric ulcers of rats created by mucosal resection: course of changes in the interleukin-1.beta. (IL-1.beta.) expression"<br>SEI MARIANNA IKA DAIGAKU ZASSHI (1998),<br>26(5), 555-563 ,1998, XP000905128<br>abstract                                     | 1-9                   |
| X          | SANDBORN, WILLIAM J.: "Preliminary report on the use of oral tacrolimus (FK506) in the treatment of complicated proximal small bowel and fistulizing Crohn's disease"<br>AM. J. GASTROENTEROL. (1997), 92(5),<br>876-879 ,1997, XP000905061<br>abstract   | 1-9                   |
| X          | HISANAGA ET AL: "Implication of nitric oxide synthase activity in the genesis of water immersion-stress induced gastric lesions in rats: the protective effects of FK-506"<br>ALIMENTARY PHARMACOLOGY & THERAPEUTICS, GB, BLACKWELL SCIENTIFIC PUBLICATIONS LTD., CAMBRIDGE,<br>vol. 10, no. 10, 1996, pages 933-940-940,<br>XP002108980<br>ISSN: 0269-2813<br>abstract | 1-9                   |
| X          | WO 98 11908 A (BRITISH BIOTECH PHARM ;WOOD LARS MICHAEL (GB); WRIGHT ANNETTE (GB))<br>26 March 1998 (1998-03-26)<br>abstract<br>page 6, paragraph 4 -page 8, paragraph 2<br>page 15, paragraph 2; claims 1-8  | 1-9                   |
|            | -/--  |                       |

## INTERNATIONAL SEARCH REPORT

International Application No.

JP 99/04978

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| X          | WO 93 18048 A (PFIZER)<br>16 September 1993 (1993-09-16)<br>abstract<br>page 2, line 10 -page 5, line 23<br>-----   | 1-7                   |
| X          | WO 93 18050 A (PFIZER)<br>16 September 1993 (1993-09-16)<br>page 2, line 11 -page 6, line 10<br>-----   | 1-7                   |
| X          | DE 43 29 503 A (GALENIK LABOR FREIBURG<br>GMBH) 2 March 1995 (1995-03-02)<br>abstract; claims 1-6<br>-----  | 1-9                   |
| X          | US 5 352 671 A (BAUMANN KARL ET AL)<br>4 October 1994 (1994-10-04)<br>abstract<br>column 25, line 49 -column 26, line 60;<br>example 66A<br>column 1, line 5<br>----- | 1-9                   |



## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claims 1-7,9 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds specifically mentioned in the claims, with due regard to the general idea underlying the present application.

Present claims 1-9 relate to compounds defined by reference to a desirable characteristic or property, namely immunosuppressant property. The claims cover all compounds/uses having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products/compounds specifically mentioned in the claims.

The Present claims 1-9 relate to a method/use defined (inter alia) by reference to the following parameter(s):  
P1: MMP production inhibitor/ treating MMP-mediated disease.  
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the "More preferable MMP-mediated diseases" (Cf. page 15 of the description), with due regard to preferable MMP-mediated diseases.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP 99/04978

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 4,6,9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

JP 99/04978

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)  | Publication<br>date  |
|---|---------------------|---|--|
| WO 9117754 A                              | 28-11-1991          | NONE  |  |
| WO 9811908 A                              | 26-03-1998          | AU 4390597 A<br>EP 0936918 A  | 14-04-1998<br>25-08-1999   |
| WO 9318048 A                              | 16-09-1993          | AT 159725 T<br>CA 2131373 A<br>DE 69314947 D<br>DE 69314947 T<br>DK 636136 T<br>EP 0636136 A<br>ES 2108261 T<br>FI 944015 A<br>GR 3025672 T<br>JP 7500350 T<br>JP 2562001 B<br>US 5631235 A   | 15-11-1997<br>16-09-1993<br>04-12-1997<br>05-03-1998<br>22-12-1997<br>01-02-1995<br>16-12-1997<br>01-09-1994<br>31-03-1998<br>12-01-1995<br>11-12-1996<br>20-05-1997   |
| WO 9318050 A                              | 16-09-1993          | AT 153027 T<br>CA 2131372 A,C<br>DE 69310721 D<br>DE 69310721 T<br>DK 629209 T<br>EP 0629209 A<br>ES 2102642 T<br>FI 944017 A<br>GR 3024048 T<br>JP 2563080 B<br>JP 7500352 T<br>MX 9301060 A<br>US 5747465 A   | 15-05-1997<br>16-09-1993<br>19-06-1997<br>04-09-1997<br>13-10-1997<br>21-12-1994<br>01-08-1997<br>01-09-1994<br>31-10-1997<br>11-12-1996<br>12-01-1995<br>01-09-1993<br>05-05-1998   |
| DE 4329503 A                              | 02-03-1995          | AU 693470 B<br>AU 7535494 A<br>CA 2170748 A<br>WO 9506464 A<br>EP 0716598 A<br>JP 9501939 T<br>NZ 271655 A  | 02-07-1998<br>22-03-1995<br>09-03-1995<br>09-03-1995<br>19-06-1996<br>25-02-1997<br>22-09-1997   |
| US 5352671 A                              | 04-10-1994          | US 5912238 A<br>AT 126803 T<br>AU 640963 B<br>AU 6584390 A<br>CA 2029694 A<br>DE 69021833 D<br>DE 69021833 T<br>DK 427680 T<br>EP 0427680 A<br>ES 2077663 T<br>GR 3017858 T<br>HK 30096 A<br>HU 210900 B<br>IE 69974 B<br>IL 96268 A<br>JP 2750302 B<br>JP 3223291 A<br>KR 166074 B | 15-06-1999<br>15-09-1995<br>09-09-1993<br>23-05-1991<br>10-05-1991<br>28-09-1995<br>21-03-1996<br>18-12-1995<br>15-05-1991<br>01-12-1995<br>31-01-1996<br>23-02-1996<br>28-09-1995<br>16-10-1996<br>23-07-1996<br>13-05-1998<br>02-10-1991<br>15-01-1999 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

JP 99/04978

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| US 5352671 A                              |                     | LV 11621 A                 | 20-12-1996          |
|   |                     | LV 11621 B                 | 20-04-1997          |
|   |                     | NZ 235991 A                | 26-05-1993          |
|   |                     | ZA 9009024 A               | 29-07-1992          |

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C.20231  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

|   |   |
|---|---|
| <b>Date of mailing</b> (day/month/year)<br>01 May 2000 (01.05.00)                 |   |
| <b>International application No.</b><br>PCT/JP99/04978                            | <b>Applicant's or agent's file reference</b><br>PWO-18725             |
| <b>International filing date</b> (day/month/year)<br>10 September 1999 (10.09.99) | <b>Priority date</b> (day/month/year)<br>14 September 1998 (14.09.98) |
| <b>Applicant</b><br>YAMAMOTO, Nobuchika et al                                     |   |

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

03 April 2000 (03.04.00)

☐ in a notice effecting later election filed with the International Bureau on:
2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

|  |  |
|--|--|
| <b>The International Bureau of WIPO</b><br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br>Facsimile No.: (41-22) 740.14.35 | Authorized officer<br>R. Forax<br>Telephone No.: (41-22) 338.83.38 |
|--|--|

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

TABUSHI, Eiji  
Fujisawa Pharmaceutical Co., Ltd.  
Osaka Factory  
1-6, Kashima 2-chome  
Yodogawa-ku, Osaka-shi  
Osaka 532-8514  
JAPON

|  |  |
|--|--|
| Date of mailing (day/month/year)<br>09 May 2000 (09.05.00) | IMPORTANT NOTIFICATION   |
| Applicant's or agent's file reference<br>PWO-18725         |  |
| International application No.<br>PCT/JP99/04978            | International filing date (day/month/year)<br>10 September 1999 (10.09.99) |

## 1. The following indications appeared on record concerning:

☒ the applicant      ☒ the inventor      ☐ the agent      ☐ the common representative

|   |                            |                          |
|---|----------------------------|--------------------------|
| Name and Address<br>SAKAI, Fumio<br>6-7, Ninomiya 2-chome<br>Tsukuba-shi<br>Ibaraki 305-0051<br>Japan | State of Nationality<br>JP | State of Residence<br>JP |
|   | Telephone No.              |                          |
|   | Facsimile No.              |                          |
|   | Teleprinter No.            |                          |

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person      ☒ the name      ☐ the address      ☐ the nationality      ☐ the residence

|  |                            |                          |
|--|----------------------------|--------------------------|
| Name and Address<br>SAKAI, Fumihiko<br>6-7, Ninomiya 2-chome<br>Tsukuba-shi<br>Ibaraki 305-0051<br>Japan | State of Nationality<br>JP | State of Residence<br>JP |
|  | Telephone No.              |                          |
|  | Facsimile No.              |                          |
|  | Teleprinter No.            |                          |

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

☒ the receiving Office      ☐ the designated Offices concerned  
☐ the International Searching Authority      ☒ the elected Offices concerned  
☐ the International Preliminary Examining Authority      ☐ other:

|  |   |
|--|---|
| <p>The International Bureau of WIPO<br/>34, chemin des Colombettes<br/>1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p> | <p>Authorized officer<br/>Sean Taylor</p> <p>Telephone No.: (41-22) 338.83.38</p> |
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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

|  |  |   |  |
|--|--|---|--|
| Applicant's or agent's file reference<br>PWO - 18725                                       |  | <b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |  |
| International application No.<br>PCT/JP99/04978  | International filing date (day/month/year)<br>10/09/1999 | Priority date (day/month/year)<br>14/09/1998  |  |
| International Patent Classification (IPC) or national classification and IPC<br>A61K31/435 |  |   |  |
| Applicant<br>FUJISAWA PHARMACEUTICAL CO., LTD et. al.                                      |  |   |  |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

|   |  |
|---|--|
| Date of submission of the demand<br><br>03/04/2000  | Date of completion of this report<br><br>29.11.2000                      |
| Name and mailing address of the international preliminary examining authority:<br><br> European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br><br>Kling, I<br><br>Telephone No. +49 89 2399 8471 |



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/JP99/04978

**I. Basis of the report**

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

**Description, pages:**

1-21 as originally filed

**Claims, No.:**

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP99/04978

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

|                               |      |  |
|-------------------------------|------|--|
| Novelty (N)                   | Yes: | Claims   |
|                               | No:  | Claims 1-9   |
| Inventive step (IS)           | Yes: | Claims   |
|                               | No:  | Claims 1-9   |
| Industrial applicability (IA) | Yes: | Claims   |
|                               | No:  | Claims 1-2 4-6, 8, 9 (see separate sheet section V, 4th paragraph) |

2. Citations and explanations  
**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The documents cited in the International Search Report are numbered D1 to D8 in the order of their listing in said Search Report. Unless otherwise indicated, reference is made to the passages cited in said Search Report.

The present application does not satisfy the criterion set forth in Articles 33(2) and 33(3) PCT because the subject-matter of Claims 1 to 9 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT) and does not involve an inventive step (Rule 65(1)(2) PCT).

D1 discloses the effect of an immunosuppressant drug (FK 506 and cyclosporin) on gingival fibroblasts. D2 discloses that the immunosuppressant FK506 selectively inhibits expression of early T cell activation genes. D3 discloses the inhibition of established lesions of collagen-induced arthritis in rats by FK 506. D4 discloses CP-123,369, a potent orally active immunosuppressive agent with efficacy comparable to that of cyclosporin A and FK-506 inhibited human T cell proliferation with an  $IC_{50} = 10.4nM$ . D5 discloses the inhibition of interleukin 6 production by adherent rheumatoid synovial cells by FK 506. D7 discloses the effect of FK 506 on arthritis development. D8 discloses the anti-ulcer effect of FK 506 whereas D9 discloses that FK 506 and cyclosporin inhibit growth factor-stimulated human keratinocyte proliferation by blocking cells in the G0/G1 phases of the cell cycle. D10 teaches that the novel ascomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion (T cell activation is crucial in the pathogenesis of psoriasis). D11 discloses the neuroprotective action of FK506, in experimental stroke. D12, D13 and D14 disclose the effect of tacrolimus hydrate (FK506) on the healing process of experimental gastric ulcers of rats and in the treatment of complicated proximal small bowel and fistulizing Crohn's disease. D15 relates to a drug combination approach to reduce the toxicity of MMP Inhibitor and/or Cyclosporin A administration in particular wherein the cyclosporin is selected from Cy A and FK506. D16 and D17 disclose macrolides of formula (I) as active immunosuppressants and are useful in treating autoimmune diseases such as rheumatoid arthritis and psoriasis in a mammal and for the treatment of resistance to transplantation and fungal infection. D18 discloses a pharmaceutical composition

comprising an immunosuppressive compound selected from Tacrolimus, cyclosporin A, deoxyspergualin or rapamycin or combination thereof. D19 discloses compounds of formula I which possess interesting pharmacological activity as antiinflammatory, immunosuppressant, antiproliferative and chemotherapeutic drug resistance reversing agents. The compound 33-epi-33chloro-FR 520 (compound of example 66a) is preferred.

For the assessment of the present claims 1-2, 4-6, 8 and 9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment or the subject-matter of claims to a method for the treatment of the human or animal body by therapy or surgery, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

#### **Re Item VIII**

##### **Certain observations on the international application**

Claim 9 claims at the same time a use, an agent, a method and a pharmaceutical composition and leaves the reader in doubt as to the category of the claim, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

## PATENT COOPERATION TREATY

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NOTICE INFORMING THE APPLICANT OF THE  
COMMUNICATION OF THE INTERNATIONAL  
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

TABUSHI, Eiji  
Fujisawa Pharmaceutical Co., Ltd.  
Osaka Factory  
1-6, Kashima 2-chome  
Yodogawa-ku, Osaka-shi  
Osaka 532-8514  
JAPON

Date of mailing (day/month/year)

23 March 2000 (23.03.00)

Applicant's or agent's file reference

PWO-18725

## IMPORTANT NOTICE

International application No.

PCT/JP99/04978

International filing date (day/month/year)

10 September 1999 (10.09.99)

Priority date (day/month/year)

14 September 1998 (14.09.98)

Applicant

FUJISAWA PHARMACEUTICAL CO., LTD. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:  
CN,JP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:  
BR,CA,EP

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on  
23 March 2000 (23.03.00) under No. WO 00/15208

## REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

## REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

J. Zahra

Telephone No. (41-22) 338.83.38

